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ADVANCES IN CARDIOVASCULAR IMAGING

Myocardial Work in Echocardiography

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Abstract: Myocardial work is an emerging tool in echocardiography that incorporates left ventricular afterload into global longitudinal strain analysis. Myocardial work correlates with myocardial oxygen consumption, and work efficiency can also be assessed. Myocardial work has been evaluated in a variety of clinical conditions to assess the added value of myocardial work compared to left ventricular ejection fraction and global longitudinal strain. This review showcases the current use of myocardial work in adult echocardiography and its possible role in cardiac pathologies.

Key Words: cardiac resynchronization therapy ■ cardiomyopathies ■ echocardiography ■ global longitudinal strain ■ myocardium ■ transcatheter aortic valve replacement

Nonstandard Abbreviations and Acronyms	
CRT	cardiac resynchronization therapy
CTRCD	cancer therapeutics–related cardiac dysfunction
FMR	functional mitral regurgitation
GCW	global constructive work
GLS	global longitudinal strain
GWE	global work efficiency
GWI	global work index
GWW	global wasted work
LVSP	left ventricular systolic pressure
NT-proBNP	N-terminal pro-B-type natriuretic peptide
STE	speckle-tracking echocardiography
TAVR	transcatheter aortic valve replacement

Cardiac imaging plays a critical role in the assessment of left ventricular (LV) function and quantification of cardiovascular response to therapy. Before the advent of modern cardiac imaging techniques, physicians relied on invasive, catheter-based assessment of LV function with ventriculograms. Pressure-volume loops, created in the cardiac catheterization laboratory, significantly advanced the understanding of cardiac function and quantified myocardial work,[1] which correlated with myocardial oxygen consumption. Pressure-volume loop analysis has

delineated important relationships among preload, afterload, and myocardial contractility. However, despite their utility, invasive pressure-volume loops are often impractical in routine clinical practice. With the development of contemporary ultrasound techniques, transthoracic echocardiography became the mainstay for the evaluation of LV function, readily assessed in the measurement of LV ejection fraction (LVEF). Although LVEF is a useful screening tool for LV function, subclinical dysfunction can be undetected or underestimated. The more sensitive technique of speckle-tracking echocardiography (STE) has emerged as a well-validated tool for the evaluation and serial comparison of LV systolic function. STE quantification of peak global longitudinal strain (GLS) can detect subclinical LV dysfunction in multiple cardiovascular conditions, including valvular heart disease, cardiotoxicity, and cardiac amyloidosis.[2–4] Although GLS provides improved quantification of LV function compared to LVEF, both measures are afterload dependent. In 2018, a novel technique incorporating LV pressure into the strain measurement on echocardiography, called myocardial work, was validated and became commercially available. Myocardial work evaluates LV performance, incorporating afterload determination using cuff blood pressure, providing a more load-independent measure compared with GLS.[5] In this review, the technical aspects and clinical utility of myocardial work are outlined, including applications in various disease states.

Noninvasive Myocardial Work

Principles of Myocardial Work

Since the original description in 1895 by Otto Frank, pressure-volume loops have been pivotal in the understanding of LV hemodynamics.[6,7] Frank seminal work described the interplay of preload, afterload, and contractility in LV myocardium in one elegant, graphical representation—the pressure-volume loop. The pressure-volume loop is created from measurements in the cardiac catheterization laboratory, and it is a rectangular representation of the phases of the cardiac cycle: isovolumic contraction, systolic ejection, isovolumic relaxation, and diastolic filling (Figure 1). The ratio of the mechanical energy imparted by the myocardium to the outgoing blood to the total energy consumption is dependent on loading conditions.[9] The slope from the start of the curve to peak pressure at the end of LV ejection represents the contractility of the heart. The area of the LV pressure-volume loop reflects stroke work and myocardial oxygen consumption.

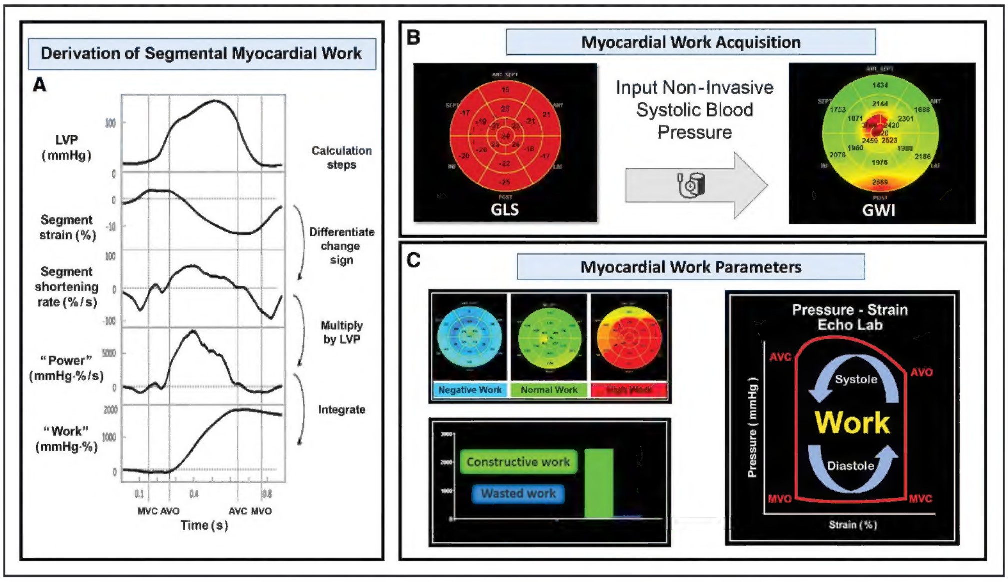

Figure 1. Myocardial work assessment overview. A, The process of segment myocardial work acquisition from initial validation paper, including the integration of noninvasive systolic blood pressure to automated functional imaging global longitudinal strain (GLS) to the final value of myocardial work (mm Hg%). Reprinted from Russell et al[8] with permission. Copyright ©2013, The American Physiological Society. **B**, Visual polar plot of a normal patient transitioning from GLS to global work index (GWI; average work calculated from pressure-strain loop). **C**, Examples of the specific data myocardial work adds from GLS. Negative, normal, and high work are assigned different colors on the polar plot. This also allows the software to calculate constructive work (positive work performed in systole and negative work during isovolumic relaxation [IVR]), wasted work (negative work during systole and positive work during IVR), and work efficiency (global constructive work [GCW]/[GCW+global wasted work]). **C**, Graphical representation of the noninvasive pressure-strain loop that is created. ANT, indicates anterior; ANT_SEPT, anteroseptal; AVC, aortic valve closure; AVO, aortic valve opening; echo lab, echocardiography laboratory; INF, inferior; LAT, lateral; LVP, left ventricular pressure; MVC, mitral valve closure; MVO, mitral valve opening; POST, posterior; and SEPT, septal.

There are 3 components of myocardial contraction. The basal and apical segments contract in opposite directions, with the subepicardium contracting in a right-handed helix and the subendocardium contracting in a left-handed helix[10]; this is circumferential strain. The myocardial fibers shorten from apex to base in systole; it is the tracking of this longitudinal shortening that is assessed with GLS. As the myocardium shortens, it also thickens—radial strain is positive—and this thickening of the myocardium in systole can be seen readily on transthoracic parasternal short-axis echocardiographic views of the LV. GLS is the most studied of the 3 components and is accurate and reproducible. The main limitation is that GLS, like LVEF, is afterload dependent. Thus, it is not possible to differentiate between abnormal GLS resulting from decreased myocardial contractility and abnormal GLS resulting from increased afterload.

A vendor-specific method (GE Healthcare, Pewaukee, WI) for assessing myocardial work was developed to include afterload in GLS analysis. Owing to the challenge of calculating myocardial force, pressure is used as a surrogate of force, and the area of the LV pressure-volume loop is used as an index of myocardial work.[11] Peak LV pressure is estimated by noninvasive cuff blood pressure.

This method was evaluated by Russell et al[11] in an experimental animal study and then confirmed in a clinical study of 24 patients. The noninvasively estimated LV pressure curve was first validated in a dog model using invasive hemodynamic monitoring under a variety of clinical conditions (left bundle branch block [LBBB] and acute myocardial infarction). Those with LBBB demonstrated markedly reduced work in the septum compared to the lateral wall (402±539 vs 1315±473 mm Hg%) by noninvasive imaging. The results of their study demonstrated a strong correlation between measured LV pressure and estimated LV pressure in the animal model during all interventions (mean r=0.99).

A subsequent study was completed on 24 patients with chronic class II to IV heart failure. Peak LV pressure was estimated using brachial artery cuff pressure in the human subject population. The LV pressure reference curve was calculated by pooling single-cycle pressure traces using the following 3 steps: (1) timing mitral and aortic valve opening and closing by echocardiography, (2) stretching or compressing raw data traces to correlate with valvular event times, and (3) stretching the traces vertically to the appropriate peak value. Similar correlation was seen in the clinical study (mean r=0.99) as the animal study. Noninvasive pressure-strain loops also showed strong correlation with regional glucose metabolism on 18-fluorodeoxyglucose positron emission tomography imaging, further supporting use of this technique for myocardial oxygen consumption.[9,11] These animal and clinical models demonstrated proof of concept, opening the door for multiple uses of noninvasive myocardial work in clinical practice.

Acquisition Steps

Myocardial work assessment is performed with a vendor-specific algorithm (GE Healthcare, Pewaukee, WI). The initial step of myocardial work acquisition is obtaining the transthoracic views for GLS analysis. The 3 standard apical views are acquired at a frame rate of >40 frames/sec with image quality adequate to visualize myocardial borders. STE is used for GLS analysis with a generated pressure curve from the duration of the isovolumic and ejection phases, as measured by the timing of aortic valve closure. Valvular event times can be assessed automatically by machine or adjusted manually through visual assessment from the apical long-axis view. Automated functional imaging is used to calculate GLS in the apical 2-, 3-, and 4-chamber long-axis views. These outlines can also be adjusted manually to conform to the myocardium. From this analysis, the bull's-eye GLS plot is generated, and GLS values are calculated and displayed.

The next step in myocardial work acquisition is the noninvasive measurement of systolic blood pressure. This is performed by measurement in the arm using a sphygmomanometer. Peak LV systolic pressure is estimated to be noninvasive systolic cuff pressure. This measurement should be performed at the time of image acquisition. This pressure is then inputted into the echocardiography machine for myocardial work analysis.

Myocardial work augments automated functional imaging with dynamic LV pressures.[12] Once blood pressure is inputted into the software, a myocardial work bull's-eye plot is created, similar to GLS. Four values are calculated: global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE).[12]

1. GWI: Average myocardial work based on the pressure-strain loop.
2. GCW: Positive work performed by a segment in systole and negative work (segment lengthening) during isovolumic relaxation.
3. GWW: Negative work (segment lengthening) during systole and positive work (segment shortening) during isovolumic relaxation.
4. GWE: GCW/(GCW+GWW).

Similar to GLS, color-coding allows the differences among high, normal, and reduced myocardial work to be visualized. Each segment can also be individually analyzed for myocardial work indices. The pressure-strain loop can be created globally and for each individual segment. Figure 1 summarizes the principles behind myocardial work acquisition and the parameters achieved. Ranges in normal healthy controls were assessed in the EACVI NORRE study (European Association of Cardiovascular Imaging Normal Reference Ranges for Echocardiography; Table 1).[13]

Table 1. Definitions of Myocardial Work (Table view)

Name	Definition	Normal range: 95% CI or confidence limits of normality±SE
GWI, mm Hg%	Total work done (area within the curve) by the ventricle during mechanical systole (MVC–MVO) including IVR	Females: 1310–2538
		Males: 1270–2428
GCW, mm Hg%	Work performed by the ventricle that contributes to LV function during systole: Longitudinal shortening of the muscle during systole and lengthening during IVR	Females: 1543–2924
		Males: 1650–2807
GWW, mm Hg%	Work performed by the ventricle that does not contribute to LV function during systole: Longitudinal lengthening of the myocardial fibers during systole plus shortening during IVR	Females: 239±39
		Males: 238±33

Name	Definition	Normal range: 95% CI or confidence limits of normality±SE
GWE (%)	Ratio of constructed work divided by sum of constructive and wasted work: GCW÷(GCW+GWW; 0%–100%)	Females: 91±1
		Males: 90±1.6

Normal ranges established in the EACVI NORRE study (European Association of Cardiovascular Imaging Normal Reference Ranges for Echocardiography).[13] GCW indicates global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; IVR, isovolumic relaxation; LV, left ventricular; MVC, mitral valve closure; and MVO, mitral valve opening.

Technical Limitations

Given that myocardial work analysis is derived from GLS analysis, the limitations of GLS acquisition also apply to myocardial work. Poor image quality inhibits speckle-tracking, and neither GLS nor myocardial work can be assessed. Atrial fibrillation and other abnormal rhythms can hinder GLS acquisition, particularly if there is excessive heart rate variability. Intra- and inter-observer variability of myocardial work is equivalent to GLS analysis—beyond GLS analysis and inputting of blood pressure, values that are generated are automatically produced by algorithm. Finally, the availability of appropriate noninvasive cuff pressure is required for myocardial work acquisition. Myocardial work analysis cannot be assessed in any clinical situation in which LV systolic pressure does not equal noninvasive systolic blood pressure; for this reason, patients with severe aortic stenosis (AS) or fixed LV outflow tract obstruction were excluded from original validation studies.

Myocardial work has several technical limitations. This analysis is strongly dependent on adequate 2-dimensional image quality. Poor image quality, low frame rates, atrial fibrillation, and tachycardia can all lead to inaccuracies in strain analysis tracking. Without quality imaging, speckle-tracking and myocardial work analysis cannot be performed. An accurate and timely brachial cuff pressure also is required for the analysis. Cuff pressure should be performed during and in the position of transthoracic imaging to ensure the blood pressure accurately correlates with the stress or afterload of the LV at the time of the images being acquired. Strain analysis may use different algorithms depending on the vendor platform being used. Currently, there is only one vendor platform with a myocardial work noninvasive algorithm. Thus, at present, myocardial work is dependent solely on this software that is available.

In addition to the technical limitations, other limitations may be patient- or pathology-dependent. Myocardial work may not be accurate in patients whose LV has undergone extensive remodeling. Pressure-volume loops do not account for direction of blood flow, a factor in patients with conditions such as significant mitral regurgitation. Myocardial work analysis does not take into account wall stress, thickness, or curvature, all components of afterload. Furthermore, the creation of the pressure-volume loop does not take into account changes in diastolic pressure. Lembo et al[14] have shown that matched cohorts with elevated diastolic blood pressure affected all indices of myocardial work, highlighting the need for future investigation. Finally, afterload, preload, and contractility are interrelated and dependent on loading conditions.

LV Myocardial Work

Hypertension

The interpretation of LVEF and GLS in the setting of hypertension is challenging given the increased afterload.[15] Increased afterload can result in reduced strain, which gives an impression of reduced LV systolic function; however, the ventricle is performing more myocardial work to maintain a similar stroke volume.

Myocardial work has been evaluated in hypertensive patients. Studies have demonstrated increased GWI in hypertensive patients. Chan et al[16] found that, compared to normotensive patients, 37 patients with hypertension had significantly higher GWI (2590±435 versus 1900±165 mm Hg%, $P<0.05$) to match increased afterload despite similar LVEF and GLS, whereas GWE remained unchanged. These data suggest that increased afterload in the setting of hypertension leads to overall increase in global myocardial work (GWI), with very little wasted work. The myocardium is not inefficient in the setting of increased afterload, but it is working harder. This finding was confirmed by a separate study in which GWI and GCW were increased in 110 hypertensive patients (with and without diabetes) compared with 55 controls.[17] Finally, GWI was observed to increase in patients with increasing stages of hypertension[18] and resistant/uncontrolled hypertension.[19] In 83 patients with hypertension, higher blood pressures within the same day also led to changes in global myocardial work.[20]

Figure 2 demonstrates increased myocardial work in a hypertensive patient with normal LVEF and normal GLS. Hypertension is a pure afterload state, and GWI and GCW increase without any significant wasted work (GWW) or loss of myocardial efficiency. Future studies that evaluate the use of serial measurement of myocardial work parameters over time will provide useful information about the clinical role of myocardial work measurement in patients with hypertension.

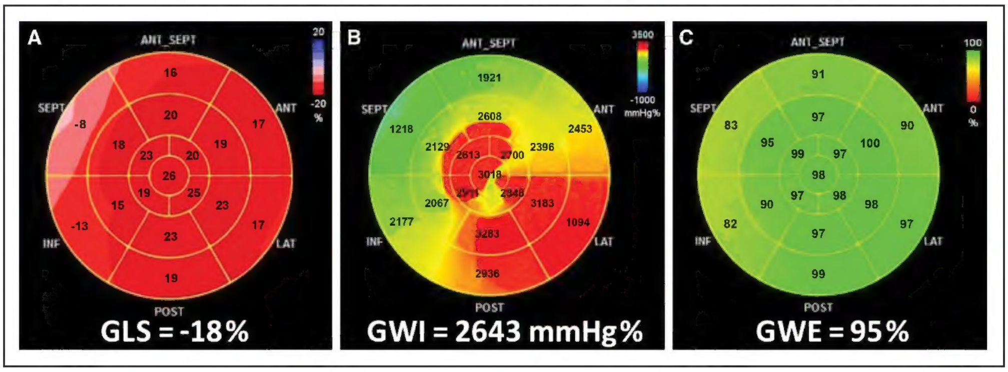

Figure 2. Hypertension. Blood pressure at the time of the echocardiogram was 165/90 mm Hg. Left ventricular ejection fraction (60%) and global longitudinal strain (GLS; −18%) are both preserved (**A**). Global work index (GWI) is elevated (2643 mm Hg%) with multiple red-shaded segments (**B**); global work efficiency (GWE) is relatively unaffected (95%), as demonstrated by all green-shaded segments (**C**). ANT indicates anterior; ANT_SEPT, anteroseptal; INF, inferior; LAT, lateral; POST, posterior; and SEPT, septal.

Coronary Artery Disease

Accurate diagnosis is critical for early detection and treatment in stable coronary artery disease (CAD) and acute coronary syndrome. Myocardial work has been studied in acute coronary syndrome and stable CAD patients. Zhang et al[21] examined the use of myocardial work indices in the detection of stable CAD. These 131 patients presented with stable chest pain and underwent myocardial work assessment and coronary angiography. Both GWI and GCW identified high-risk stable CAD accurately with good sensitivity and specificity. Furthermore, the regional myocardial work in each major coronary artery territory showed excellent diagnostic performance in predicting high-risk CAD. Boe et al[22] found that regional myocardial work was superior to all other echocardiographic parameters (LVEF and GLS) in detecting acute coronary occlusion in patients presenting with non–ST-segment–elevation myocardial infarction. The presence of >4 adjacent

segments with myocardial work of <1700 mm Hg% was able to detect occlusive CAD with a sensitivity of 81% and a specificity of 82%.[22] In a similar study, Jin et al[23] found that myocardial work was a potential tool for the detection of microvascular dysfunction in post–ST-segment–elevation myocardial infarction patients. In a study of 115 patients with an ejection fraction ≥55% who were referred for coronary angiography, patients with significant CAD had significantly reduced GWI (*P*<0.001).[24] GLS was reduced (*P*<0.001) in patients with multivessel CAD but not in those with single-vessel disease (*P*=0.47).[24] Thus, GWI was a more sensitive measure than GLS in patients with no regional wall motion abnormalities and a normal LVEF.[24] Also, a GWI value ≤1810 mm Hg% has a positive predictive value of 95% in the detection of significant CAD.[24]

Myocardial work may also provide prognostic value for patients with CAD. In a study of 88 consecutive patients undergoing multivessel percutaneous coronary intervention, echocardiography was performed 3 months postintervention. Patients with reverse remodeling had significantly lower GWI, GCW, and GWE, and significantly higher GWW (*P*<0.05).[25] Liu et al[25] suggested a GCW cutoff of 1438.5 mm Hg% as a predictor of early LV remodeling (sensitivity 85%, specificity 70%).

Figure 3 demonstrates an example of ischemic heart disease and its effect on myocardial work assessment. The patient had ischemic cardiomyopathy with severely reduced ejection fraction and regional wall motion abnormalities. GLS and GWI were both significantly reduced. The polar plots showcase the regional variability in myocardial work and work efficiency.

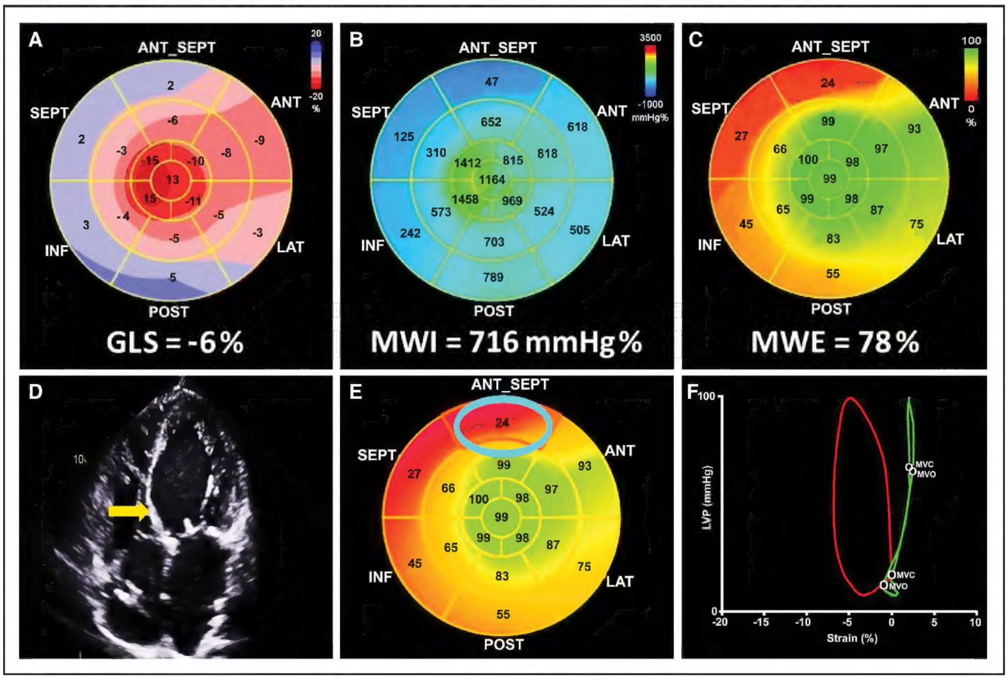

Figure 3. **Coronary artery disease.** Left ventricular systolic function is significantly reduced (ejection fraction 24%) with regional wall motion abnormalities, including a septum that is akinetic and scarred with relatively preserved apical contractility. Global longitudinal strain (GLS) is markedly reduced (−6%; **A**) as is global work index (GWI; 716 mm Hg%), which demonstrates very low amounts of work being performed, especially in the septal region shown by dark blue segments (**B**). Global work efficiency (GWE; 921 mm Hg%/[921 mm Hg%+251 mm Hg%]) is also abnormal (78%), with the lowest efficiency in the septal segments, as demonstrated by red-colored shading (global constructive work=921 mm Hg% and global wasted work=251 mm Hg%; **C**). The apical 4-chamber view at end-systole demonstrates severely decreased left ventricular function with a thin, akinetic septum (**D**). Segmental analysis of the anterior septum demonstrates an abnormal pressure-strain loop of the affected myocardium (**E** and **F**). ANT indicates anterior; ANT_SEPT, anteroseptal; INF, inferior; LAT, lateral; LVP, left ventricular pressure; MVC, mitral valve closure; MVO, mitral valve opening; MWE, myocardial work efficiency; MWI, myocardial work index; POST, posterior; and SEPT, septal.

Fewer studies have been performed on the role of myocardial work with exercise stress echocardiography. GLS has been used to help improve diagnostic accuracy but is not universally performed in stress echocardiography. In a retrospective study of 60 patients with normal stress echocardiograms, myocardial work increased postexercise and GWE was preserved.[26] In patients with inducible ischemia, a lower baseline global and regional myocardial work was observed, myocardial work decreased further in myocardial segments supplied by a stenosed coronary artery postexercise, and GWE decreased significantly (P=0.0002). These findings suggest that myocardial work has potential uses in routine stress echocardiography to help providers evaluate for ischemic response to exercise. Additional research is needed to determine the clinical utility of myocardial work in the diagnosis, prognostication, and management of CAD.

Dyssynchrony

LV dyssynchrony significantly worsens morbidity and mortality among heart failure patients with widened QRS on electrocardiogram because different regions of the myocardium contract at different times, resulting in reduced mechanical performance of the ventricle.[27] Cardiac resynchronization therapy (CRT) has been shown to reduce morbidity and mortality in these patients.[28–30] Although early assessments focused on QRS duration, multiple trials, including the CARE-HF study (Cardiac Resynchronization — Heart Failure) showed that direct assessment of mechanical dyssynchrony was superior to QRS duration alone in identifying responders to CRT.[31] As a result, several imaging techniques have been developed to directly assess mechanical dyssynchrony.

Although cardiac magnetic resonance imaging (MRI) and single-photon emission computed tomography provide useful tools for assessment of dyssynchrony,[32,33] echocardiography is the test of choice for direct assessment of mechanical dyssynchrony. In 2002, Pitzalis et al[34] demonstrated the use of M-mode for measurement of septal to posterior wall motion delay to predict CRT response.[35] Later, more advanced novel techniques such as tissue Doppler imaging allowed for direct measurement of myocardial velocity, comparison of multiple myocardial segments, and evaluation of mechanical activation pattern—parameters that proved useful in identifying responders to CRT.[36,37] Later, strain and strain rate measurements derived from tissue Doppler imaging permitted the assessment of active deformation compared with passive motion and allowed for the assessment of synchrony in patients with large scar burden. Although this technique was promising, tissue Doppler imaging–derived strain and strain rate parameters could not identify responders to CRT.[38] Tissue Doppler imaging strain was succeeded by 2-dimensional STE strain, which provided angle-independent assessment of myocardial deformation. Multiple studies have demonstrated successful prediction of CRT response using the 2-dimensional STE-derived parameters of radial strain,[39] longitudinal strain, and longitudinal strain delay index.[40]

In 2012, Russell et al[11] published a method for the quantification of energy loss in dyssynchronous ventricles. They sought to better understand and quantify how much LV work was wasted in dyssynchronous ventricles by stretching opposing segments that were not actively involved in contraction. With the introduction of myocardial work, Russell et al[8] studied 20 healthy controls, 10 patients with LBBB, and 9 patients with LBBB and CRT. They demonstrated that in patients with LBBB, there was significant wasted work (controls: 0.09±0.03, LBBB: 0.36±0.16) and that when CRT was introduced, wasted work was subsequently reduced (0.36±0.16 versus 0.17±0.07, P<0.001). Figure 4 demonstrates a case of a dyssynchronous LV with abnormal regional myocardial work in the anterior septum. Vecera et al[41] built on Russell et al's[8] findings and showed that wasted work in the septum together with wall motion score index was a strong

predictor of CRT response (area under the curve, 0.86 [95% CI, 0.71–1.0]) and that GWW significantly decreased in 21 patients after receiving CRT (39±21 versus 17±7%, *P*=0.0015). Lastly, a recent study employed assessment of myocardial work in the evaluation of left bundle branch area pacing as a promising alternative to traditional biventricular CRT in 62 heart failure patients. Left bundle branch area pacing showed greater improvement in GWI, and also in GWE, compared with biventricular pacing as well as in the setting of improved mechanical synchronization.[42] Further work is needed to examine the relationship between clinical outcomes and CRT timing in patients with dyssynchronous ventricles.

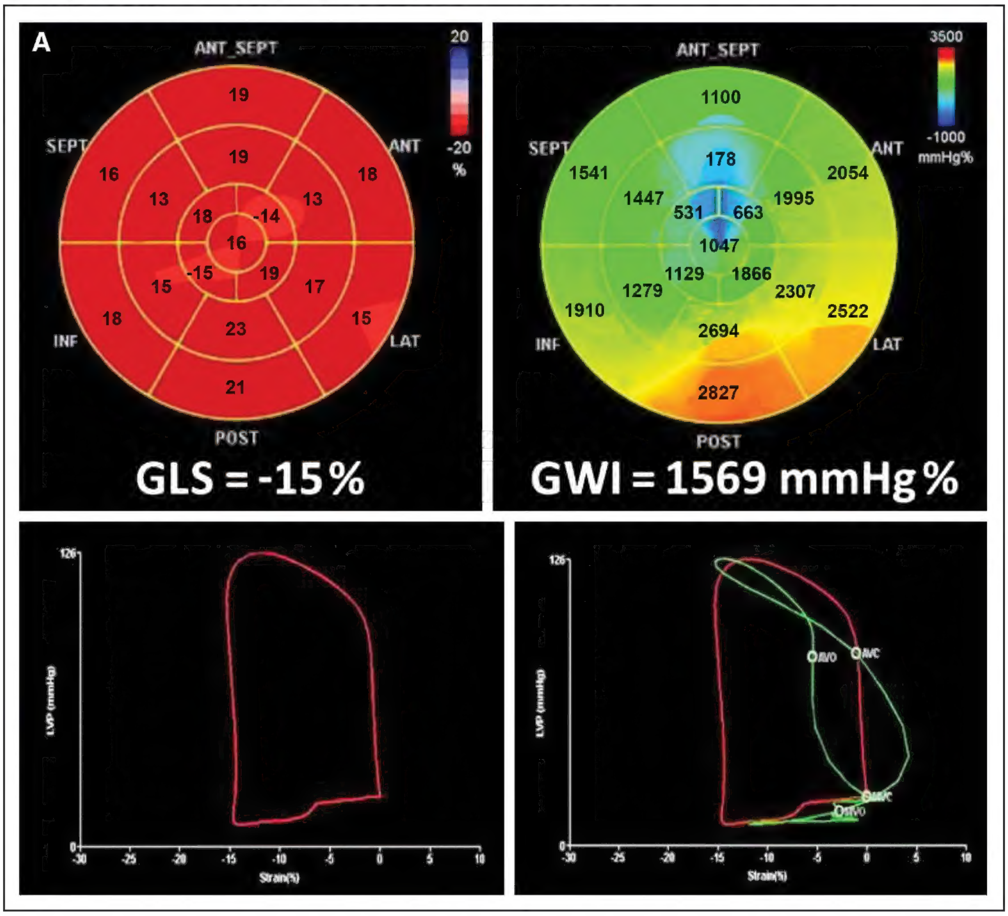

Figure 4. **Dyssynchrony.** Global longitudinal strain (GLS) is abnormal (−15%; **A**); global work index (GWI) is mildly abnormal (1569 mm Hg%), with the lowest amount of work in the mid and apical anteroseptal segments, demonstrated by blue shading, and high amounts of work taking place in the basal posterior and lateral segments, demonstrated by red shading (**B**). Pressure-strain loop of the GWI (**C**) compared with the pressure-strain loop of the anteroseptal apical segment, which is demonstrated by the green loop that has a smaller area and twisted appearance (**D**). ANT indicates anterior; ANT_SEPT, anteroseptal, AVC, aortic valve closure; AVO, aortic valve opening; INF, inferior; LAT, lateral; LVP, left ventricular pressure; MVC, mitral valve closure; MVO, mitral valve opening; POST, posterior; and SEPT, septal.

Hypertrophic Cardiomyopathy and Athlete's Heart

Hypertrophic cardiomyopathy and athlete's heart share phenotypic features on echocardiography. Differentiating between adaptive hypertrophy and cardiomyopathy can be challenging.[43] GLS, radial strain, and LV twist have been evaluated as ways to differentiate athlete's heart from cardiomyopathy; however, there has not been consensus on the utility of strain in this population.[44–47] Reduced GLS is common in hypertrophic cardiomyopathy patients and correlates with fibrosis on cardiac MRI.

Recently, myocardial work has shown potential utility in the quantification of LV systolic function in patients with hypertrophic cardiomyopathy. Galli et al[48] demonstrated that GCW is significantly reduced in patients with nonobstructive hypertrophic cardiomyopathy compared with healthy

controls. Their study further showed that GCW is associated with significant fibrosis on cardiac MRI (odds ratio [OR], 1.01 [95% CI, 0.99–1.08]; *P*=0.04). This finding was also observed by Goncalves et al[49] in a study in which a cutoff of ≤1550 mm Hg% of GCW was associated with ≥15% late gadolinium enhancement on cardiac MRI with a sensitivity of 91% and a specificity of 84%. A study by Hiemstra et al[50] demonstrated that the reduction in myocardial work parameters seen in patients with nonobstructive hypertrophic cardiomyopathy was significantly associated with worse long-term outcomes. In this study, patients with a GCW >1730 mm Hg% had better event-free survival (*P*<0.001). Myocardial work is a useful tool in all variants of hypertrophic cardiomyopathy. Figure 5 highlights a patient with apical hypertrophic cardiomyopathy with a small apical pouch. Regional myocardial work shows negative (wasted) work taking place in the apex, even in this patient with normal LVEF.

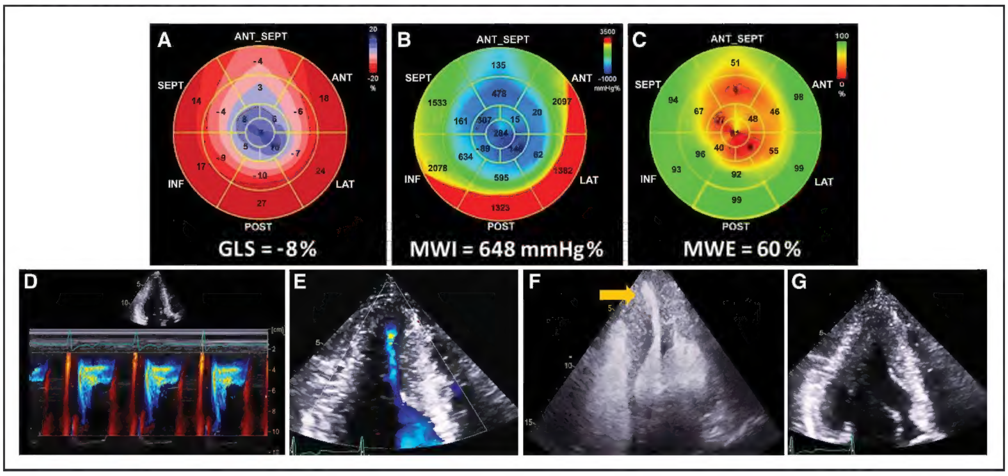

Figure 5. Apical hypertrophic cardiomyopathy. Global longitudinal strain (GLS) is significantly reduced (-8%) with the typical predominantly blue-shaded apex (**A**). Global work index (GWI) is significantly decreased (648 mm Hg%) with negative amounts of work, demonstrated by dark blue shading, taking place in the apex, and very high amounts of work, demonstrated by red shading, in the basal posterior and lateral segments (**B**). Global work efficiency (GWE) is also very abnormal (60%), with the lowest amount of efficiency, demonstrated by red shading, in the apical and midanteroseptal segments (**C**). A small apical pouch is demonstrated on color flow with turbulent flow on color M-mode through the septum (**D** and **E**). Severe apical hypertrophy with apical pouch is confirmed with echo enhancement (**F** and **G**). ANT indicates anterior; ANT_SEPT, anteroseptal; INF, inferior; LAT, lateral; POST, posterior; and SEPT, septal.

In contrast to hypertrophic cardiomyopathy, the LV hypertrophy seen in athletes represents an adaptive change to training conditions. Increased end-diastolic volume with normal or even slightly reduced LVEF is observed; with exertion, LVEF greatly increases in athletes. Myocardial work may allow for improved measurement of LV function because it accounts for afterload, which is commonly reduced in endurance athletes. A study by D'Andrea et al[51] compared STE strain and myocardial work in 350 endurance athletes with 150 healthy controls. They found that although resting LV GLS was significantly reduced in endurance athletes compared with controls (−18.4±2.6 versus −22.4±3.3%; *P*<0.01), GWE was not significantly different. Further, GWE at rest was closely related to maximal watts, peak VO_2, and LV E/e′ measured at peak exertion. Regular exercise training was associated with decreased GLS but increased GWI at rest, and GWI was positively correlated with VO_2/kg.[52] These studies suggest that GWI at rest may more accurately predict the performance of the athlete's heart than other markers of LV systolic function.

Amyloidosis

With advancements in cardiac imaging, cardiac amyloidosis is more readily diagnosed in the echocardiography laboratory. STE has been a reliable tool in the evaluation of possible cardiac amyloid, with relative apical sparing being a sensitive and specific marker of cardiac

amyloidosis.[53] Myocardial work has also been evaluated in these patients. Clemmensen et al[54] showed that patients with cardiac amyloidosis had significantly reduced GWI and GWE compared with controls. With exertion, GWE decreased significantly in patients with cardiac amyloid, which might suggest inefficient energy usage in patients with cardiac amyloid.[54] Compared with relative wall thickness or relative apical sparing measured by GLS, myocardial work had lower accuracy in diagnosing transthyretin cardiac amyloidosis but was significantly correlated with NT-proBNP (N-terminal pro-B-type natriuretic peptide) and troponin.[55] Further studies showed that GWI was correlated with NT-proBNP, mortality, and peak oxygen consumption in patients with cardiac amyloid; however, it did not perform better than GLS.[56] In contrast, Clemmensen et al[57] found that global myocardial work was predictive of major adverse cardiac events and all-cause mortality, whereas GLS was not. The use of myocardial work indices in cardiac amyloidosis deserves further study to determine the precise role in clinical management. Figure 6 shows a case of cardiac amyloidosis with increased LV wall thickness. The patient had the classical apical sparing GLS pattern seen in amyloidosis. GWI demonstrated the normal work being done at the apex and negative work at the base.

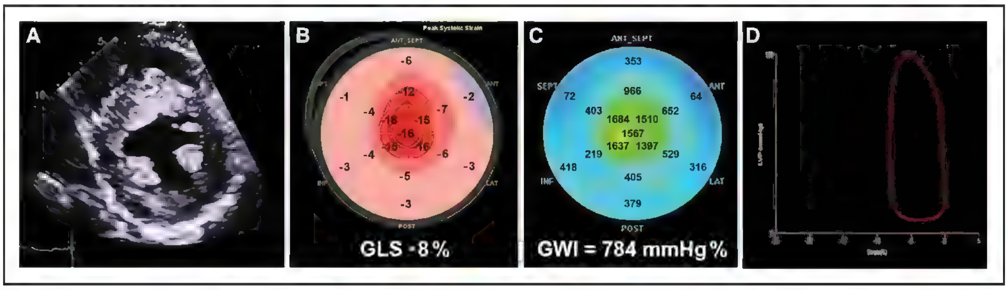

Figure 6. Cardiac amyloidosis. Echocardiography demonstrates severely thickened left ventricular walls measuring 2.4 cm (**A**). A bull's-eye plot of strain from the same patient demonstrates the typical apical sparing seen in amyloid heart disease (**B**). A bull's-eye plot of myocardial work in the same patient shows decreased global work index (GWI; 784 mm Hg%) with normal work at the apex and negative work at the base (**C**). A narrow pressure-strain loop from the same patient is shown (**D**). ANT indicates anterior; ANT_SEPT, anteroseptal; GLS, global longitudinal strain; INF, inferior; LAT, lateral; LVP, left ventricular pressure; POST, posterior; and SEPT, septal.

Dilated Cardiomyopathy

The ability to accurately characterize LV function is important for patients with dilated cardiomyopathy to assess prognosis, adjust therapies, and monitor for deterioration. GLS has been shown to predict prognosis more accurately than LVEF in patients with heart failure.[58–60] The use of pressure-volume loops in the evaluation of dilated cardiomyopathy is relatively new. Invasive and cardiac MRI evaluation of pressure-volume loops demonstrated reduced myocardial work in patients with dilated cardiomyopathy compared with controls.[61] Noninvasive echocardiographic evaluation of myocardial work has recently been explored as a method to assess LV performance in patients with dilated cardiomyopathy.

Chan et al[16] evaluated patients with ischemic and nonischemic dilated cardiomyopathy and found that both groups had reduced GWI, increased GWW, and reduced GWE. Furthermore, patients with dilated cardiomyopathy demonstrated significantly elevated end-systolic wall stress. GWI, GCW, and GWE were all better predictors of fibrosis on cardiac MRI than GLS in a study by Cui et al.[62] Hedwig et al[63] demonstrated that GWI and GCW were predictive of a combined endpoint of all-cause mortality, implantation of an LV assist device, or heart transplantation in a group of patients with advanced heart failure. One observational study found that treatment with sacubitril/valsartan significantly improved GCW and GWE.[64] Further studies evaluating myocardial work parameters in patients with dilated cardiomyopathy are needed to understand the ability of

this technique to characterize myocardial performance and track changes over time in response to natural disease progression and therapeutic interventions. Figure 7 highlights a patient with known dilated cardiomyopathy with severely decreased GWI and an abnormal pressure-strain loop consistent with severe LV dysfunction.

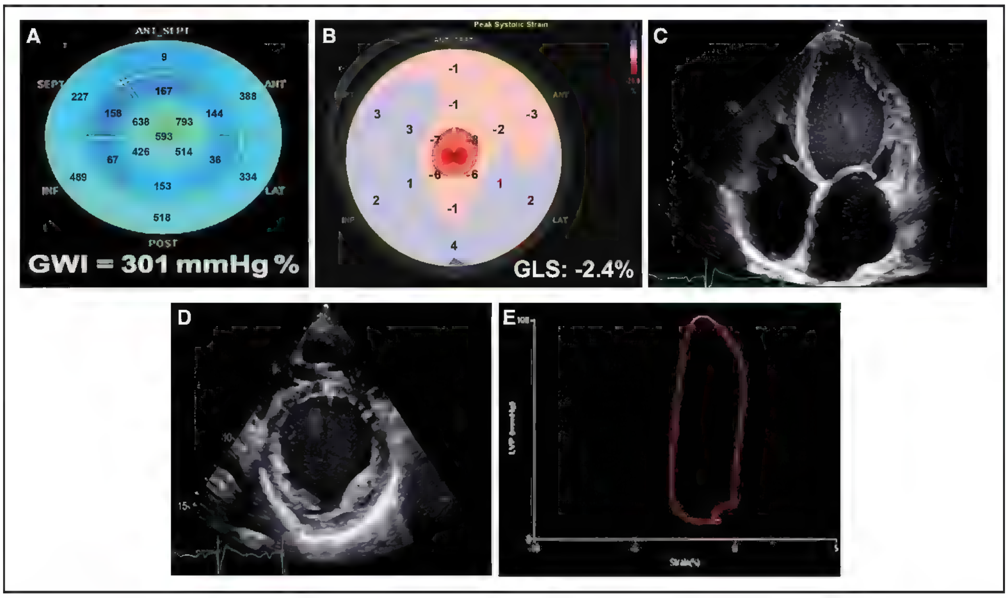

Figure 7. Nonischemic cardiomyopathy. A bull's-eye plot demonstrates severely decreased global work index (GWI; 301 mm Hg%; **A**). A bull's-eye plot for the same patient correlates with a severely reduced global longitudinal strain (GLS) of −2.4% (**B**). The apical 4-chamber (**C**) and parasternal short-axis (**D**) views at end-systole show the severely dilated left ventricle with severely reduced global left ventricular dysfunction. The pressure-strain loop is also markedly abnormal (**E**). ANT indicates anterior; ANT_SEPT, anteroseptal; INF, inferior; LAT, lateral; LVP, left ventricular pressure; POST, posterior; and SEPT, septal.

Cardio-Oncology

As the field of oncology is ever expanding, with new therapeutic agents being developed daily, cardio-oncology has become a complex specialty. GLS has demonstrated superiority over LVEF in the detection and management of cancer patients who develop cancer therapeutics-related cardiac dysfunction (CTRCD).[65] Serial assessment of GLS in addition to LVEF is the standard of care; however, GLS is load dependent and differences in systolic blood pressure among echocardiograms is a significant limitation of serial comparisons. A review on subclinical cardiotoxicity and the emerging role of myocardial work proposed that myocardial work could play a promising role in patients with cancer who are at increased risk of cardiotoxicity.[66] The few studies in breast cancer patients have shown mixed results with myocardial work. A study performed by Guan et al[67] compared myocardial work and GLS in breast cancer patients receiving different treatments. The most notable finding of the study was that GWI and GWE were decreased after the sixth cycle, whereas GLS showed a significant change after the fourth cycle, indicating that GLS is still a sensitive indicator of cardiac dysfunction. Calvillo-Argüelles et al[68] studied 136 HER2+ breast cancer patients receiving anthracycline and trastuzumab therapy, concluding that myocardial work indices did not offer any measurable improvement over GLS and clinical risk factors in predicting CTRCD identified at subsequent visits. They did find that in a small subset of patients with a GLS change (<3.3%) and a systolic blood pressure reduction (>21 mm Hg), myocardial work indices were associated with a higher probability of concurrent CTRCD than GLS. Kosmala et al[69] investigated the ability of myocardial work indices to differentiate changes in GLS that were related to chemotherapy versus afterload changes. Patients were divided into 4 groups based on CTRCD and blood pressure. The results demonstrated that patients who were CTRCD+ without an increase in blood pressure showed much larger decreases in GWI and GCW.

The authors found that the impairment of GLS in the presence of an increase in GWI and GCW indicated the impact of elevated afterload on LV performance in the absence of actual myocardial dysfunction. Li et al[70] studied HER2+ breast cancer patients undergoing pertuzumab and trastuzumab therapy. GLS, GWI, GCW, and GWE were significantly reduced after 4 cycles of therapy and detected toxicity in a more timely and sensitive manner than LVEF. However, it is unknown whether the change in myocardial parameters was equivalent to the occurrence of myocardial toxic events. Vaz Ferreira et al[71] investigated myocardial work before and after treatment in breast cancer patients receiving anthracycline and/or anti-HER therapy. All myocardial work indices were impaired at 4 to 6 months and tended to return to baseline at 12 to 14 months. Patients presenting with CTRCD revealed a significant decrease in GWI and GWE at 4 to 6 months compared with those without CTRCD. The utility of myocardial work indices compared to conventional echocardiographic parameters was also studied in a cohort of children and young adults (598 patients) receiving anthracycline therapy. In this study, Zhan et al[72] observed that indices of myocardial work provided an earlier and more sensitive marker of progression toward chemotherapy-related cardiac dysfunction than traditional measures, such as LVEF and GLS.

More studies are needed to determine the clinical value of myocardial work in the field of cardio-oncology and CTRCD. It is also still unknown whether a myocardial work–centered approach reduces the long-term risk of heart failure and improves clinical outcomes.

Valvular Heart Disease

Aortic Stenosis

AS is a disease of both the valve and the LV myocardium, which attempts to compensate for the fixed obstruction. LVEF is often preserved initially, and yet GLS is frequently abnormal in severe AS. This suggests subclinical myocardial dysfunction even in the presence of normal LVEF. An abnormal GLS has been associated with poor clinical outcomes in patients with severe AS; even after correction of AS, GLS abnormalities persist in a subset of patients.[73] Thus, abnormal GLS identifies subclinical LV dysfunction, likely representing a later phase of the disease process in which LV compensatory mechanisms have already failed.

In this setting, myocardial work has been assessed in AS with some promise. GLS and LVEF are both afterload dependent. In the initial validation of myocardial work analysis, patients with severe AS were excluded as systolic blood pressure could not be used as a surrogate for LV systolic pressure (LVSP) in the setting of fixed obstruction. Jain et al[74] investigated the noninvasive assessment of LVSP by studying 35 patients in the cardiac catheterization laboratory who presented for transcatheter aortic valve replacement (TAVR); they directly measured LVSP, brachial cuff pressure, left radial arterial pressure, and echocardiographic parameters. This work demonstrated that a noninvasive method for assessing LVSP in severe AS (systolic blood pressure+mean aortic gradient) closely correlated to invasively measured LVSP (r=0.92). Fortuni et al[75,76] showed similar correlation in 120 patients with severe AS who underwent TAVR (intraclass correlation coefficient, 0.846 [95% CI, 0.781–0.891]; P<0.001). Hubert et al[77] mentioned that caution is needed when extrapolating the proposed algorithm as ventricular pressure obtained by this method is not tested against invasive LV pressure curves. This group proposed a mathematical model to estimate myocardial work noninvasively with echocardiography-specific LV pressure curves.[78] In comparing mathematical modeling to the echocardiography-based algorithm, they concluded that the algorithm had high degrees of

correlation (r^2>0.66 for GWI, GCW, GWW, and GWE) and would be easier and more appropriate for clinical practice.[79]

The use of myocardial work in severe AS is illustrated in Figure 8, depicting improvement in GLS and reduction in myocardial work after surgical aortic valve replacement. The use of myocardial work may also clarify 2 severe AS phenotypes: patients with abnormal GLS and high myocardial work and those with abnormal GLS and reduced myocardial work;[80] the latter group may represent more permanent LV dysfunction. De Rosa et al[81] showed reduced GWI (*P*<0.001) and GCW (*P*<0.001) postintervention, similar to that seen by Jain et al. Jain et al[74] showed GWI and GCW were reduced from pre-TAVR to post-TAVR (GWI: 1856.2±704.6 versus 1534.8±385.0 mm Hg%, *P*<0.001; GCW: 2102.1±797.4 versus 1815.8±441.6 mm Hg%, *P*=0.012).[74] De Rosa et al[81] also found that low-flow, low-gradient AS patients had no improvement in GWI post-TAVR.[81] Lastly, Ilardi et al[82] recently studied the prognostic value of myocardial work in AS patients. They showed increased GWI, GCW, and GWW in AS patients compared with controls and also reported that reduced GWI (hazard ratio [HR], 0.998 [95% CI, 0.997–1.000]; *P*=0.034) and GCW (HR, 0.998 [95% CI, 0.997–0.999]; *P*=0.003) measurements after follow-up were significantly associated with excess mortality. Further studies are required to evaluate the utility of myocardial work indices in severe AS in risk stratification and postintervention clinical outcomes.

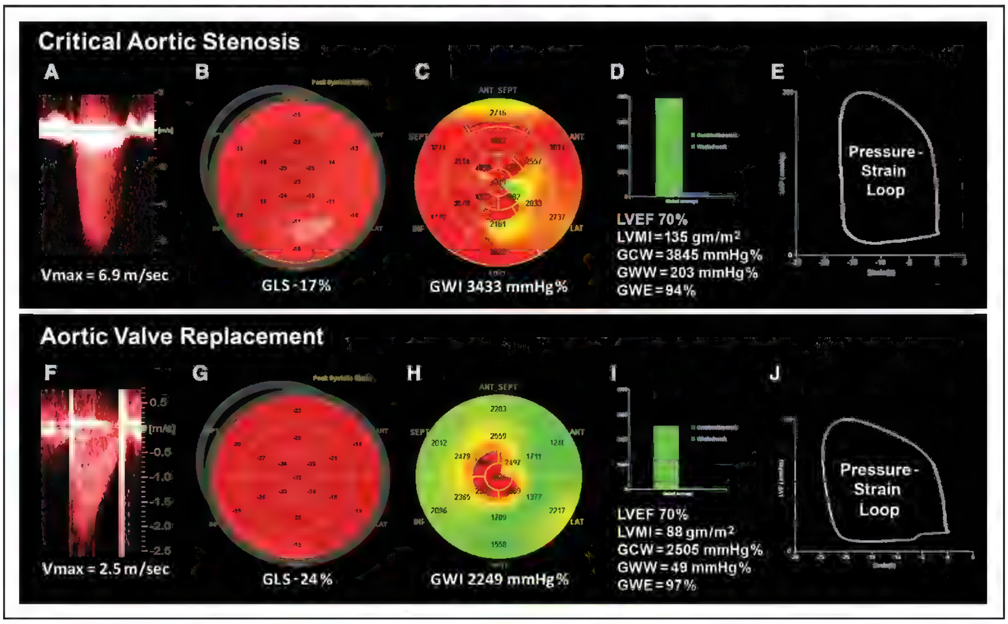

Figure 8. **Case example of patient with critical aortic stenosis.** The patient's mean gradient is 121 mm Hg and aortic valve area is 0.5 cm² (**A**). Left ventricular ejection fraction (LVEF) is preserved at 70%. Global longitudinal strain (GLS) is abnormal (−17%; **B**). Calculated global work index (GWI) demonstrated increased work, with a GWI of 3433 mm Hg% (**C**). **D** and **E**, Breakdown of myocardial work, with a global work efficiency (GWE) of 94% and a model of the pressure-strain loop. **F** through **J**, Same patient after aortic valve replacement with improvement in all variables demonstrated. ANT indicates anterior; ANT_SEPT, anteroseptal; GCW, global constructive work; GWW, global wasted work; INF, inferior; LAT, lateral; LVMI, left ventricular mass index; LVP, left ventricular pressure; POST, posterior; SEPT, septal; and Vmax, maximum velocity. Reprinted from Jain et al[80] with permission. Copyright ©2021, Elsevier.

Aortic Regurgitation

Chronic aortic regurgitation (AR) patients can remain asymptomatic for a long time before onset of symptoms. The assessment of LV dysfunction plays an important role in decision-making about asymptomatic AR patients. In a study conducted in 151 patients with severe, asymptomatic AR, D'Andrea et al[83] showed that baseline GLS and GWE were significantly reduced with normal LVEF when compared to healthy controls (GLS: −15.8±2.8% versus −21.4±4.4%, *P*<0.001, GWE: 87.1±3.3 versus 94.4±4.1%, *P*<0.001, LVEF: 57.1±4.1% versus 58.3±5.5%, *P*=not significant).

Recently, Meucci et al[84] studied 57 patients with chronic, severe AR and preserved LVEF who underwent surgical aortic valve replacement. Baseline LVEF was normal with normal to increased GWI and GCW (LVEF: 59.7±4.4%, GWI: 2084±483 mm Hg%, GCW: 2482±525 mm Hg%). GWI and GCW were positively correlated with markers of AR severity, effective regurgitant orifice area, and regurgitant volume. Furthermore, surgical aortic valve replacement resulted in a decrease in GWI, GCW, and GWE. They also found that postoperative impaired GWI was associated with adverse LV reverse remodeling, identifying a threshold of 1285 mm Hg% for GWI as a predictor (area under the curve, 0.790 [95% CI, 0.651–0.929]; *P*=0.001). Myocardial work has the potential to provide guidance on optimal timing for intervention in AR to prevent postoperative myocardial dysfunction.[85]

Mitral Valve Disease

Functional mitral regurgitation (FMR), by definition, is a consequence of LV dysfunction that interferes with mitral valve function. Myocardial work may provide additional information about LV performance in patients with FMR. Myocardial work has been studied in FMR patients in association with outcomes and survival.[86,87] Yedidya et al[86] investigated myocardial work and its association with survival in 373 patients with various grades of FMR. GWI, GCW, and GWW were significantly lower and GWE was significantly higher in patients with severe FMR than in patients with mild FMR. These parameters were independently associated with worse long-term survival (GWI ≤500 mm Hg%, GCW ≤750 mm Hg%, and GWW <300 mm Hg%). Verbeke et al[87] assessed myocardial work in 181 patients with heart failure and FMR. GWI and GLS were independently associated with cardiovascular mortality and hospitalization for heart failure (GWI: HR, 0.927, *P*=0.034, GLS: HR, 0.884, *P*=0.015). However, GWI did not outperform GLS (delta −2 log likelihood=0.8, *P*=0.37). Myocardial work also has been evaluated in patients with FMR treated with percutaneous edge-to-edge mitral valve repair.[88,89] Hubert et al[88] showed at 6-month follow-up in 56 patients that GCW improved significantly postintervention, whereas LVEF and GLS remained the same (GCW: 977±366 versus 1101±404 mm Hg%, *P*=0.003, LVEF: 33±6 versus 33±13%, *P*=0.78, GLS: −9.8%±4 vs -9.9±3.9, *P*=0.84). In patients with LVEF <35% undergoing percutaneous mitral valve repair, GWI was associated with a poor outcome (area under the curve, 0.882, *P*=0.009). Papadopoulos et al[89] reported a significant increase in GWI and GCW postintervention in 86 patients. Baseline LVEF, GLS, GWI, and GCW were associated with a reduction of LV end-diastolic volume 1 year after intervention, and baseline GCW was associated with a reduction in LV end-systolic volume (*P*<0.05 for all). Yedidya et al[90] divided 70 FMR patients into 2 groups: improvers (improvement in forward stroke volume index ≥20%) and nonimprovers (forward stroke volume index <20%). GWI and GCW worsened in nonimprovers (*P*=0.005 and *P*=0.004, respectively), whereas no difference was seen in improvers (*P*=0.093 and *P*=0.112, respectively). GWE was associated with forward stroke volume index improvement postintervention, independent of LV systolic function. Despite the advantage of myocardial work, pressure-strain analysis does not differentiate between forward and regurgitant volume, which remains a limitation in FMR.[91]

Myocardial Work and COVID-19

Myocardial work recently has been studied during and after recovery from COVID-19 infection. Minhas et al[92] reported that reduced GWE was associated with increased in-hospital mortality

(OR, 0.92 [95% CI, 0.85–0.99]; P=0.048). Lairez et al[93] reported that GWE was decreased in COVID-19 infection and that troponin-T levels during admission correlated with GWE (r=−0.383, P=0.009). Another study on patients with COVID-19 and elevated hs-troponin found low GWI (1930 versus 2132 mm Hg%, P=0.028) at an average of 4.3 months (interquartile range, 3.5–5.3) after discharge.[94]

Ikonomidis et al[95] showed that, after COVID-19 recovery, patients at 4 months had increased GWW (P=0.01) and decreased GWE (P=0.006) and GLS (P<0.05), with improvement at 12 months (P=0.043, P=0.001, P=0.069, respectively); however, these remained impaired compared to controls. In another study, Luchian et al[96] reported that patients with dyspnea presented with reduced GLS (P=0.039), GCW (P=0.024), and GWI (P=0.030) compared with asymptomatic patients and that GCW and GWI were independently associated with dyspnea (OR, 0.998 [95% CI, 0.997–1.000], P=0.035; OR, 0.998 [95% CI, 0.997–1.000], P=0.040).

Right Ventricular Myocardial Work

Measures of right ventricular function have been a clinical challenge. Multiple echocardiographic parameters are currently used to evaluate right ventricular function, including tricuspid annular plane systolic excursion, fractional area change, and S′. All of these have their technical limitations and inconsistencies. Right ventricular myocardial work has been performed in limited studies using the same algorithm. Butcher et al[97] demonstrated that RV GCW demonstrated a moderate correlation with invasively measured stroke volume and stroke volume index (r=0.63, P=0.002 and r=0.59, P=0.004) in 22 heart failure patients with reduced ejection fraction. In a follow-up study from the same group, Butcher et al[98] looked at the association of right ventricular myocardial work indices and all-cause mortality in 51 pulmonary hypertension patients and 21 patients with no structural heart disease. They showed that right ventricular GCW (HR, 1.42 per 100 mm Hg% <900 mm Hg% [95% CI, 1.12–1.81]; P=0.004) and right ventricular GWI (HR, 1.46 per 100 mm Hg% <650 mm Hg% [95% CI, 1.09–1.94], P=0.010) were associated with all-cause mortality, whereas conventional parameters of right ventricular function were not. These studies were performed using GLS and myocardial work software designed for the LV—dedicated right ventricular myocardial work software and validation is an area for future development.

Conclusions

The critical question is whether myocardial work offers incremental value over GLS and/or LVEF in clinical disease states. A summary of current data is listed in Table 2. Although a significant increase in the number of papers has been seen in the past 4 years, large-scale studies are still awaited. Central questions need to be answered: Is increased myocardial work a risk factor for heart failure? Does decreased myocardial work correlate with morbidity and mortality in patients with nonischemic cardiomyopathy? Does myocardial work improve with guideline-directed medical therapy in heart failure patients? Larger studies, pooled data, and longer-term follow-up will help elucidate these clinical questions.

Table 2. Current Status of Myocardial Work in Clinical Practice (Table view)

Pathology	Myocardial work
Hypertension	GWI and GCW increase with increased afterload (HTN) whereas GLS and LVEF remain unchanged.[16,17]
	GWI increases incrementally along with each stage of HTN.[18]
Coronary artery disease	Regional myocardial work superior to LVEF and GLS in detecting acute coronary occlusion in patients presenting with NSTEMI.[22]
	GWI value of ≤1810 mm Hg% has a positive predictive value of 95% in the detection of significant coronary artery disease.[24]
	Regional myocardial work decreases in areas supplied by stenosed arteries during stress echocardiography with decreased GWE.[26]
Dyssynchrony	Patients with LBBB have significantly higher amounts of wasted work which improves with CRT.[8]
	Wasted work in the septum+wall motion score index is a strong predictor of CRT response.[41]
Hypertrophic cardiomyopathy	GCW is significantly reduced in patients with hypertrophic cardiomyopathy.[48]
	GCW ≤1550 mm Hg% is associated with ≥15% late gadolinium enhancement on cardiac MRI.[49]
	GCW >1730 mm Hg% is associated with better event-free survival.[50]
Amyloidosis	GWI found to be superior to GLS in predicting major adverse cardiac events and all-cause mortality.[57]
Dilated cardiomyopathy	GWI, GCW, and GWE are better predictors of fibrosis on MRI than GLS.[62]
	GWI and GCW found to be predictors of all-cause mortality and need for LV assist device implantation/transplantation.[63]
Cardio-oncology	Myocardial work indices associated with a higher probability of concurrent CTRCD than GLS in small subset of patients with >21 mm Hg systolic blood pressure reduction and a GLS change (<3.3%).[68]
Valvular heart disease	GWI, GCW, and GWW increased in aortic stenosis patients. Reduced GWI and GCW at follow-up are associated with increased mortality.[82]
	GWI and GCW positively correlate with aortic regurgitation severity in patients with normal LVEF.[84] GWI threshold of 1285 mm Hg% is a predictor of LV reverse remodeling.[84]
	Reduced GWI, GCW, and GWW associated with worse long-term survival in patients with severe functional mitral regurgitation.[86] GCW improves after transcatheter edge-to-edge repair (whereas GLS and LVEF did not).[88]
COVID-19	Reduced GWE is associated with increased in-hospital mortality with COVID-19 infections.[92]

CRT indicates cardiac resynchronization therapy; CTRCD, cancer therapeutics-related cardiac dysfunction; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; HTN, hypertension; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; and NSTEMI, non–ST-segment–elevation myocardial infarction.

Noninvasive myocardial work is a promising new tool for the evaluation of LV systolic function to help differentiate reduced myocardial performance due to increased afterload versus reduced myocardial contractility. The improved detection of subclinical cardiac dysfunction may be a powerful surrogate of disease that will improve our mechanistic understanding of cardiac disease, help identify potential therapeutic targets, and offer opportunities for early diagnosis. The proper use and interpretation of myocardial work will be important for incorporating these measures into clinical practice. Future research should focus on new clinical applications of myocardial work, gathering long-term outcomes data, and examining the use of myocardial work to track cardiovascular response to therapy.

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